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EXAMINER	
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1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,973	CERTA ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,8-15,18 and 22-43* is/are pending in the application.

4a) Of the above claim(s) *15,18 and 22-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 8-14, 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1, 4, 8-14, 18, 22-43 are currently pending in the instant application.

In response to a previous Office action, a non-final requirement (mailed on October 12, 2006), Applicants filed a response and amendment received on February 14, 2007, amending claims 1, 4, 8-9, and 13 and canceling claims 2-3, 5-7, 16-17, 19-21 is acknowledged. Claims 18, and 22-42 remain withdrawn as drawn to nonelected invention.

Claims 1, 4, 8-14 and 43 are under consideration and will be examined herein.

Applicants' arguments filed on February 14, 2007, have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Maintained Claim objection

Previous objection of claim 10 for encompassing non-elected subject matter is maintained, as applicants do not amend the claim and no argument.

Maintained - Claim Rejections - 35 U.S.C. § 112 (1st)

Previous rejection of claims 1, 4, 8-12, 14 and 43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been described at length in previous

Office Actions. Applicant's amendments to claims 1, 4, 8-9, and 13 and canceling claims 2-3, 5-7, 16-17, 19-21 and arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims 1, 4, 8-12, 14 and 43 are directed to a genus of any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4 polypeptide.

Applicants argue that the claims have been amended to recite a long form PDE4 polypeptide sequence with an amino-terminal deletion wherein the polypeptide sequence starts at any amino acid located between LF1 splice site and the first amino acid of the UCR1 of the native long form PDE4 polypeptide and the specification provides support for the claims as amended. Applicants also argue that as the sequences of the native PDE4 polypeptides are known; the lengths of the specifically claimed species are specified by position of the starting amino acid, and since a person skilled in the art knows in vitro methods to produce amino-terminal deletion mutants, e.g., site directed mutagenesis, and applicants submit that the claims as amended are supported and enabled by the specification.

Applicant's arguments and amendments to claims have been fully considered but are not deemed to be persuasive to overcome the rejection on Written description issues.

Examiner acknowledges addition of some limitations in claim 1, however the amendment does not give enough structural feature of any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4 protein, which is required for fulfilling written description requirements i.e. structure and function. Applicants amendment to claim 1 in the

recitation "a long form PDE4 polypeptide sequence with an amino-terminal deletion wherein the polypeptide sequence starts at any amino acid located between LF1 splice site and the first amino acid of the UCR1 of the native long form PDE4 polypeptide", wherein no sequence is presented in said claim and regarding "long form", there are many long form PDE4 or PDE4D known in the art, and claims still read on any long from without any structural feature. Furthermore, the recitation "polypeptide starts at any amino acid located between the long form splice site and UCR1, which are hypothetical without any specific structural feature Applicants are advised to provide specific structural feature i.e. amino acid sequence of said modified polypeptide, which will overcome the rejection.

As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art,

adequate written description of a genus, which embraces widely variant species, cannot be achieved by disclosing only one species within the genus. The specification teaches a single representative species of unmodified PDE i.e. SEQ ID NO: 1. The genus of polypeptide of PDE is structurally diverse as it broadly encompasses many mutants and variants comprising phosphodiesterase activity having different structures. As such, the disclosure solely of functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Previous rejection of Claims 1, 4, 8-12, 14 and 43 under 35 U.S.C. 112, first paragraph, on scope of enablement issues is maintained. This rejection has been described in length in previous Office Actions. Applicant's amendments and arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims 1, 4, 8-12, 14 and 43 are directed to a genus of any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4D3.

Applicants argue that the claims have been amended to recite a long form PDE4 polypeptide sequence with an amino-terminal deletion wherein the polypeptide sequence starts at any amino acid located between LF1 splice site and the first amino acid of the UCR1 of the native long form PDE4 polypeptide and the specification provides support for the claims as amended. Applicants also argue that as the sequences of the native PDE4 polypeptides are known; the lengths of the specifically claimed species are specified by position of the starting amino acid, and since a person skilled in the art knows in vitro methods to produce amino-

terminal deletion mutants, e.g., site directed mutagenesis, and applicants submit that the claims as amended are supported and enabled by the specification.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1, 4, 8-12, 14 and 43 on scope of the enablement issues.

Claims 1, 3-4 and 10 are so broad as to encompass any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PDE or splice variants PDE4D including mutants and variants broadly encompassed by the claims. The claims still read on any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4D3 as well as "a long form PDE4 polypeptide sequence with an amino-terminal deletion wherein the polypeptide sequence starts at any amino acid located between LF1 splice site and the first amino acid of the UCR1 of the native long form PDE4 polypeptide", which does not specify a concrete structural feature rather a broad structural feature. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in the instant case the disclosure is limited to the amino acid sequence of only one unmodified PDE4 protein. The specification

clearly requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of PDE4 have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 from any source having an amino terminal deletion or one or more amino acid (serine) substitutions to any PDE4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any modified phosphodiesterase PDE4 or any isoform of PDE4D or any PDE4D3 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore, the rejection is maintained.

New-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bolger et al. (A family of human phosphodiesterases homologous to the dunce learning and memory gene product of Drosophila melanogaster are potential targets for antidepressant drugs, Mol Cell Biol. 1993 Oct;13(10):6558-71, see IDS). Instant Claims are directed to a modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion, wherein polypeptide sequence start any amino acid located between LF1 splice site and UCR1, wherein said polypeptide having decreased aggregation characteristics, wherein said polypeptide is PED4D3.

Bolger et al. teach one isoform of human PDE4D polypeptide including N-terminal truncation (see p6564, Col 2, 3rd paragraph, and Fig. 1) of PDE4D as well as alternatively spliced variant such as PDE4D3 polypeptide, having cAMP-specific phosphodiesterase activity. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE4, having a splice site (LF1) and upstream conserved region (UCR1 and UCR2). Bolger et al. furthermore teach expression of a truncated version of said PDE4D3 protein in which the expressed protein begin at the F residue immediately following the LF1 splice site of the native PDE4D3 polypeptide. Therefore, Bolger et al. anticipate claims 1, 4, 8 and 10 of the instant application.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4 and 10 are rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (Characterization of five different proteins produced by alternatively spliced mRNAs from the human cAMP-specific phosphodiesterase PDE4D gene, Biochem J. 1997 Dec 1; 328 (Pt 2): 539-48) in view of Kenan et al. (Functions of the N-terminal region of cyclic nucleotide phosphodiesterase 3 (PDE 3) isoforms, J Biol Chem. 2000 Apr 21; 275(16): 12331-8). Instant Claims 1 and 4 are directed to a modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion, wherein polypeptide sequence start any amino acid located between LF1 and UCR1, wherein said polypeptide having decreased aggregation characteristics, wherein said polypeptide is PED4D.

Bolger et al. teach one isoform of human PDE4D polypeptide including N-terminal deletion (1-78 amino acid) (see page 543, column 2) PDE4D as well as alternatively spliced variant such as PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of

instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated but 93% soluble in NaCl+Triton-X-100 solution. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE4, having a splice site (LF1) and upstream conserved region (UCR1 and UCR2). Bolger et al. furthermore teach that several amino acid residues upstream of UCR1 is the start site of native PDE4D polypeptide. Bolger et al. do not teach start site of said polypeptide between splice site of LF1 and UCR1 region and enhance solubility characteristics due to N-terminal deletion.

Kenan et al. teach PDE3, wherein N-terminal portion of phosphodiesterase (PDE) 3 i.e. region 1 (amino acids 1-300), which contains a large hydrophobic domain with six predicted transmembrane helices, and region 2 (amino acids 301-500), with a smaller hydrophobic domain (approximately 50 residues) as well as full-length human (H) PDE3A and mouse (M) PDE3B and a series of N-terminal truncated mutants, wherein activities of HPDE3A, H3A-Delta189, MPDE3B, and M3B-Delta196, which retained all or part of the hydrophobic domain in region 1, were recovered almost entirely in particulate fractions i.e. insoluble. Kenan et al. also teach that H3A-Delta321 (1-321 deletion) and M3B-Delta302, containing region 2, were recovered essentially equally in particulate (insoluble) and cytosolic fractions (soluble), H3A-Delta397 and H3A-Delta457, lacking both hydrophobic domains, were predominantly cytosolic (completely soluble) and H3A-Delta510 and M3B-Delta604, lacking both regions 1 and 2, were virtually completely cytosolic. Furthermore, Kenan et al. teach that with removal of greater amounts of N-terminal sequence, aggregation of PDE3 decreased. These results suggest that the hydrophobic domains in regions 1 and 2 contain structural determinants important for association of PDE3

with intracellular membranes, as well for self-association or aggregation during gel filtration and sensitivity to a specific inhibitor.

Bolger et al. clearly discusses that it is only long form PDEs that partition to the insoluble fraction (see particularly Fig. 3) such that a skilled artisan would clearly have an expectation that whatever sequences are responsible for partitioning to the insoluble fraction are in the N-terminal region as this is the portion which differs among various isoforms. This clearly would motivate one to make deletions of particularly this region to improve the solubility.

Therefore, it would have been obvious to one to ordinary skill in the art at the time of the invention was made to combine the teachings of Bolger et al. and Kenan et al. to make a N-terminal deleted PDE4 of Bolger et al. such that start site resides between LF1 splice site and UCR1 region by using mutagenesis techniques and using the method of Kenan et al. for producing N-terminal deleted PDE4 protein having reduced aggregation properties.

One of ordinary skill in the art would have been motivated for using N-terminal deleted PDE4 protein having reduced aggregating characteristics as Kenan et al. clearly showed that deleting N-terminal hydrophobic regions renders the distribution of said protein in cytosolic i.e. highly soluble and having less aggregating characteristics.

One of ordinary skill in the art would have a reasonable expectation of success because Kenan et al. successfully showed a method of producing less aggregating PDE43 by deleting N-terminal hydrophobic region.

Therefore, claims 1 and 4 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claims 11-13 are rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1997, see IDS) in view of Kenan et al. (2000, see IDS) as applied to claims 1, 4 and 10 as discussed above, further in view of MacKenzie et al. (Long PDE4 cAMP specific phosphodiesterases are activated by protein kinase A-mediated phosphorylation of a single serine residue in Upstream Conserved Region 1 (UCR1), Br J Pharmacol. 2002 Jun; 136(3): 421-33).

Bolger et al. teach one isoform of human PDE4D polypeptide including N-terminal deletion (1-78 amino acid) (see page 543, column 2) PDE4D as well as alternatively spliced variant such as PDE4D3 polypeptide, which is 100% identical to the PDE4D3 sequence of instant application having cAMP-specific phosphodiesterase activity. Bolger et al. also teach that PDE4D3 is a membrane bound (very firmly) PDE, which is not soluble in aqueous buffer i.e. 95% insoluble or aggregated but 93% soluble in NaCl+Triton-X-100 solution. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE4, having a splice site (LF1) and upstream conserved region (UCR1 and UCR2). Bolger et al. furthermore teach that several amino acid residues upstream of UCR1 is the start site of native PDE4D polypeptide. Bolger et al. do not teach start site of said polypeptide between splice site of LF1 and UCR1 region and enhance solubility characteristics due to N-terminal deletion.

Kenan et al. teach PDE3, wherein N-terminal portion of phosphodiesterase (PDE) 3 i.e. region 1 (amino acids 1-300), which contains a large hydrophobic domain with six predicted transmembrane helices, and region 2 (amino acids 301-500), with a smaller hydrophobic domain (approximately 50 residues) as well as full-length human (H) PDE3A and mouse (M) PDE3B and a series of N-terminal truncated mutants, wherein activities of HPDE3A, H3A-Delta189,

MPDE3B, and M3B-Delta196, which retained all or part of the hydrophobic domain in region 1, were recovered almost entirely in particulate fractions i.e. insoluble. Kenan et al. also teach that H3A-Delta321 (1-321 deletion) and M3B-Delta302, containing region 2, were recovered essentially equally in particulate (insoluble) and cytosolic fractions (soluble), H3A-Delta397 and H3A-Delta457, lacking both hydrophobic domains, were predominantly cytosolic (completely soluble) and H3A-Delta510 and M3B-Delta604, lacking both regions 1 and 2, were virtually completely cytosolic. Furthermore, Kenan et al. teach that with removal of greater amounts of N-terminal sequence, aggregation of PDE3 decreased. These results suggest that the hydrophobic domains in regions 1 and 2 contain structural determinants important for association of PDE3 with intracellular membranes, as well for self-association or aggregation during gel filtration and sensitivity to a specific inhibitor.

However, MacKenzie et al. teach one or more mutation of serine residues of PDE4D3 polypeptide, wherein serine at position 54 (Ser54) is mutated to alanine residue. MacKenzie et al. also teach serine residue at position 579 in PDE4D3 polypeptide. Mackenzie et al. also suggest that inhibiting PKA-specific activation of PDE, which might improve cognitive function, asthma, depression, and stroke or cardiac reperfusion injury.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Bolger et al. (1997) and Kenan et al. and Mackenzie et al. to introduce a mutation at Ser54 on N-terminal deleted PDE protein made obvious by the combined disclosures Bolger et al. and Kenan et al. by using the methods of mutating serine residues specially serine at position 54 (Ser54) to alanine residue as taught by

Mackenzie et al. to make a PDE polypeptide, which is resistant to phosphorylation at position 54 by PKA as determine by phospho-serine54 specific antibody.

One of skilled artisan would have been motivated to mutate serine 54 position to alanine of PDE4D3 of Bolger et al. and Kenan et al., since Ser54 is the phosphorylation site of protein kinase A, which leads to decrease PDE activity thereby reduce the breakdown of cAMP, which is a strong signaling mediator that may inhibit cellular desensitization processes in cells, thereby enhance cell to cell communication through cAMP signal transduction machinery, which might have beneficial role on improving cognitive function, asthma, depression, stroke or cardiac reperfusion injury.

One of the skilled artisans would have a reasonable expectation of success of mutating Ser54 by well-known mutagenesis techniques as McKenzie et al. successfully made a PDE4D3 mutated of serine residues at 54 and 579 positions to enhance cell-to-cell communication through cAMP.

Applicants argue that Bolger et al. fails to describe or suggest a PDE4 polypeptide having its N-terminal start between the LF1 splice site and the first amino acid of the UCR1 domain as required by the instant claims and MacKenzie et al. describes native PDE4D3 polypeptides in which the serine atom at position 54 is mutated to alanine. Furthermore, applicants argue that MacKenzie does not describe or suggest PDE4 polypeptides having the N-terminus between the LF1 splice site and the first amino acid of the UCR1 domain. Thus, MacKenzie et al. does not overcome the deficiency of Bolger et al., and the combination of Bolger et al. and MacKenzie et al. cannot render the instant claims obvious.

Applicant's arguments have been fully considered and new references (Bolger, 1997 and Kenan et al. 2000) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claims 11-13 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claims 11-13 rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1993, see IDS) in view of MacKenzie et al. (2002). Instant claims are directed to a modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion, wherein polypeptide sequence start any amino acid located between LF1 and UCR1, wherein said polypeptide having decreased aggregation characteristics and having mutation at serine residues particularly Ser54, wherein said polypeptide is PED4D.

Bolger et al. teach one isoform of human PDE4D polypeptide including N-terminal truncation (see p6564, Col 2, 3rd paragraph, and Fig. 1) of PDE4D as well as alternatively spliced variant such as PDE4D3 polypeptide, having cAMP-specific phosphodiesterase activity. Bolger et al. further teach the said protein is a long form polypeptide among the splice variants or isoform of PDE4, having a splice site (LF1) and upstream conserved region (UCR1 and UCR2). Bolger et al. furthermore teach expression of a truncated version of said PDE4D3 protein in which the expressed protein begin at the F residue immediately following the LF1 splice site of the native PDE4D3 polypeptide. Therefore, Bolger et al. anticipate claims 1, 4, 8 and 10 of the instant application.

However, MacKenzie et al. teach one or more mutation of serine residues of PDE4D3 polypeptide, wherein serine at position 54 (Ser54) is mutated to alanine residue. MacKenzie et al. also teach serine residue at position 579 in PDE4D3 polypeptide. Mackenzie et al. also suggest that inhibiting PKA-specific activation of PDE, which might improve cognitive function, asthma, depression, and stroke or cardiac reperfusion injury.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to combine the teachings of Bolger et al. (1993), and Mackenzie et al. to introduce a mutation at Ser54 on N-terminal deleted PDE protein of Bolger et al. by using the methods of mutating serine residues specially serine at position 54 (Ser54) to alanine residue as taught by Mackenzie et al. to make a PDE polypeptide, which is resistant to phosphorylation at position 54 by PKA as determine by phospho-serine54 specific antibody.

One of skilled artisan would have been motivated to mutate serine 54 position to alanine of PDE4D3 of Bolger et al. (1993), since Ser54 is the phosphorylation site of protein kinase A, which leads to decrease PDE activity thereby reduce the breakdown of cAMP, which is a strong signaling mediator that may inhibit cellular desensitization processes in cells, thereby enhance cell to cell communication through cAMP signal transduction machinery, which might have beneficial role on improving cognitive function, asthma, depression, stroke or cardiac reperfusion injury.

One of the skilled artisans would have a reasonable expectation of success of mutating Ser54 by well-known mutagenesis techniques as McKenzie et al. successfully made a PDE4D3 mutated of serine residues at 54 and 579 positions to enhance cell-to-cell communication through cAMP.

Applicant's arguments have been fully considered and new references (Bolger, 1993 and Kenan et al. 2000) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claims 11-13 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claim 14 is rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1997, see IDS) in view of Kenan et al. (2000, see IDS) as applied to claims 1, 4 and 10 as discussed above, further in view of Bifulco et al. (2',3'-Cyclic nucleotide 3'-phosphodiesterase: a membrane-bound, microtubule-associated protein and membrane anchor for tubulin, Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1807-12. Epub 2002 Feb 12). Claim 14 is directed to any modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion between any amino acid located between LF1 and UCR1, wherein the polypeptide exhibits decreased tubulin association, wherein said PDE4 protein having decreased aggregation characteristics.

Bolger et al (1997) and Kenan et al. were discussed above and make obvious a truncated long form PDE4 as explained. However Bolger and Kenan do not teach a truncated long form PDE4 having decreased association with tubulin.

However, Bifulco et al. teach a cAMP-specific phosphodiesterase, which is firmly associated with tubulin through C-terminal region of PDE and enhance microtubule assembly. Bifulco et al. further teach the association of PDE and tubulin could be reduced by phosphorylation of the phosphodiesterase protein by PKC or deletion of C-terminus of phosphodiesterase protein, which results in interference of phosphodiesterase and tubulin

association. Bifulco et al. also teach the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent.

One of ordinary skilled in the art would have been motivated for reducing PDE and tubulin association because the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent for therapeutic purpose.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to check whether there is any interaction between the N-terminal deleted PDE polypeptide as taught by Bolger et al. (1997) and Kenan et al. (2000), and tubulin or role of PDE on tubulin assembly formation or polymerization as taught by Bifulco et al. Bifulco et al. clearly show the interaction between PDE and tubulin through C-terminal region of PDE and deleting PDE at C-terminal region or phosphorylation of PDE protein results in the reduced PDE and tubulin association.

Applicants argue that Bolger et al. fails to describe or suggest a PDE4 polypeptide having its N-terminal start between the LF1 splice site and the first amino acid of the UCR1 domain as required by the instant claims and Bifulco et al. also does not describe or suggest PDE4 polypeptides having the N-terminus between the LF 1 splice site and the first amino acid of the UCR1 domain. Furthermore, applicants argue that Bifulco et al. does not overcome the deficiency of Bolger et al., and the combination of Bolger et al. and Bifulco et al. cannot render the instant claims obvious.

Applicant's arguments have been fully considered and new references (Bolger, 1993 and Kenan et al. 2000) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claim 14 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claim 14 rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1993, see IDS) in view of Bifulco et al. (2',3'-Cyclic nucleotide 3'-phosphodiesterase: a membrane-bound, microtubule-associated protein and membrane anchor for tubulin, Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1807-12. Epub 2002 Feb 12). Instant claim is directed to a modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion, wherein polypeptide sequence start any amino acid located between LF1 and UCR1, wherein said polypeptide having decreased aggregation characteristics, which exhibits decreased tubulin association, wherein said polypeptide is PED4D.

Bolger et al (1993) was discussed above and teaches a truncated long form PDE4 as explained. However Bolger et al. do not teach a truncated long form PDE4 having decreased with tubulin.

However, Bifulco et al. teach a cAMP-specific phosphodiesterase, which is firmly associated with tubulin through C-terminal region of PDE and enhance microtubule assembly. Bifulco et al. further teach the association of PDE and tubulin could be reduced by phosphorylation of the phosphodiesterase protein by PKC or deletion of C-terminus of phosphodiesterase protein, which results in interference of phosphodiesterase and tubulin association. Bifulco et al. also teach the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent.

One of ordinary skilled in the art would have been motivated for reducing PDE and tubulin association because the association between PDE and tubulin cause tubulin polymerization, which results in cancer for developing anticancer agent for therapeutic purpose.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to check whether there is any interaction between the N-terminal deleted PDE polypeptide as taught by Bolger et al. (1993) and tubulin or role of PDE on tubulin assembly formation or polymerization as taught by Bifulco et al. Bifulco et al. clearly show the interaction between PDE and tubulin through C-terminal region of PDE and deleting PDE at C-terminal region or phosphorylation of PDE protein results in the reduced PDE and tubulin association.

Applicant's arguments have been fully considered and new references (Bolger, 1993 and Kenan et al. 2000) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claim 14 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claim 43 rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1997, see IDS) in view of Kenan et al. (2000, see IDS) as applied to claims 1, 4 and 10 as discussed above further in view of in view of Lee et al. (Crystal structure of phosphodiesterase 4D and inhibitor complex (1), FEBS Lett. 2002 Oct 23; 530(1-3): 53-8). Claim 43 is directed to any modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion between any amino acid located between LF1 and UCR1, wherein the polypeptide is crystallized, wherein said PDE4 protein having decreased aggregation characteristics.

Bolger et al (1997) and Kenan et al. were discussed above and make obvious a truncated long form PDE4 as explained. However Bolger and Kenan do not teach a truncated long form PDE4 in a crystallized form.

However, Lee et al. teach a crystal structure of cAMP-specific phosphodiesterase, specifically isoform PDE4D.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to produce a crystal structure of N-terminal deleted PDE protein of Bolger et al. and Kenan et al. and by using the method of Lee et al. to produce a crystallized PDE polypeptide to understand the molecular structure of N-terminal deleted PDE for targeting that polypeptide by inhibitors for therapeutic intervention against specific diseases caused by active PDE proteins.

One of ordinary skill in the art would have a reasonable expectation of success in crystallizing an N-terminal deleted PDE protein by the method of Lee et al. because the PDE proteins of Lee et al. and Bolger et al. are structurally very closely related such that a skilled artisan would expect them to have similar crystallization properties. As such the rejection is maintained.

Applicants argue that Bolger et al. fails to describe or suggest a PDE4 polypeptide having its N-terminal start between the LF1 splice site and the first amino acid of the UCR1 domain as required by the instant claims and Lee et al. also does not describe or suggest PDE4 polypeptides having the N-terminus between the LF 1 splice site and the first amino acid of the UCR1 domain, crystalline or otherwise. Furthermore, Applicants argue hat Lee et al. does not overcome the deficiency of Bolger et al., and the combination of Bolger et al. and Lee et al. cannot render the instant claims obvious.

Applicant's arguments have been fully considered and new references (Bolger, 1993 and Kenan et al. 2000) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claim 43 would have been prima *facie* obvious to use of ordinary skill in the art.

New-Claim Rejections - 35 USC § 103

Claim 43 rejected under 35 U.S.C. 103(a) as being obvious over Bolger et al. (1993, see IDS) in view of Lee et al. (Crystal structure of phosphodiesterase 4D and inhibitor complex (1), FEBS Lett. 2002 Oct 23; 530(1-3): 53-8). Instant claim is directed to a crystallized structure of modified phosphodiesterase PDE4 polypeptide having an amino terminal deletion, wherein polypeptide sequence start any amino acid located between LF1 and UCR1, wherein said polypeptide having decreased aggregation characteristics, which exhibits decreased tubulin association, wherein said polypeptide is PED4D.

Bolger et al (1993) was discussed above and teaches a truncated long form PDE4 as explained. However Bolger does not teach a truncated long form PDE4 in a crystallized form.

However, Lee et al. teach a crystal structure of cAMP-specific phosphodiesterase, specifically isoform PDE4D.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to produce a crystal structure of N-terminal deleted PDE protein of Bolger et al. by using the method of Lee et al. to produce a crystallized PDE polypeptide to understand the molecular structure of N-terminal deleted PDE for targeting that polypeptide by inhibitors for therapeutic intervention against specific diseases caused by active PDE proteins.

One of ordinary skill in the art would have a reasonable expectation of success in crystallizing an N-terminal deleted PDE protein by the method of Lee et al. because the PDE proteins of Lee et al. and Bolger et al. are structurally very closely related such that a skilled artisan would expect them to have similar crystallization properties. As such the rejection is maintained.

Applicants argue that Bolger et al. fails to describe or suggest a PDE4 polypeptide having its N-terminal start between the LF1 splice site and the first amino acid of the UCR1 domain as required by the instant claims and Lee et al. also does not describe or suggest PDE4 polypeptides having the N-terminus between the LF 1 splice site and the first amino acid of the UCR1 domain, crystalline or otherwise. Furthermore, Applicants argue hat Lee et al. does not overcome the deficiency of Bolger et al., and the combination of Bolger et al. and Lee et al. cannot render the instant claims obvious.

Applicant's arguments have been fully considered and new reference (Bolger, 1993) will make obvious a truncated long form of PDE4 as explained, which will fulfill the concern raised by the applicants regarding truncated form of PDE4.

Therefore, claim 43 would have been prima *facie* obvious to use of ordinary skill in the art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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